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Detection of ISUP ≥2 prostate cancers using multiparametric MRI: prospective multicentre assessment of the non-inferiority of an artificial intelligence system as compared to the PI-RADS V.2.1 score (CHANGE study)

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ABSTRACT

Introduction Prostate multiparametric MRI (mpMRI) has shown good sensitivity in detecting cancers with an International Society of Urological Pathology (ISUP) grade of ≥2. However, it lacks specificity, and its inter-reader reproducibility remains moderate. Biomarkers, such as the Prostate Health Index (PHI), may help select patients for prostate biopsy. Computer-aided diagnosis/detection (CAD) systems may also improve mpMRI interpretation. Different prototypes of CAD systems are currently developed under the Recherche Hospitalo-Universitaire en Santé / Personalized Focused Ultrasound Surgery of Localized Prostate Cancer (RHU PERFUSE) research programme, tackling challenging issues such as robustness across imaging protocols and magnetic resonance (MR) vendors, and ability to characterise cancer aggressiveness. The study primary objective is to evaluate the non-inferiority of the area under the receiver operating characteristic curve of the final CAD system as compared with the Prostate Imaging-Reporting and Data System V.2.1 (PI-RADS V.2.1) in predicting the presence of ISUP ≥2 prostate cancer in patients undergoing prostate biopsy.

Methods This prospective, multicentre, non-inferiority trial will include 420 men with suspected prostate cancer, a prostate-specific antigen level of ≤30 ng/mL and a clinical stage ≤T2 c. Included men will undergo prostate mpMRI that will be interpreted using the PI-RADS V.2.1 score. Then, they will undergo systematic and targeted biopsy. PHI will be assessed before biopsy. At the end of patient inclusion, MR images will be assessed by the final version of the CAD system developed under the RHU PERFUSE programme. Key secondary outcomes include the prediction of ISUP grade ≥2 prostate cancer during a 3-year follow-up, and the number of biopsy procedures saved and ISUP grade ≥2 cancers missed by several diagnostic pathways combining PHI and MRI findings.

Ethics and dissemination Ethical approval was obtained from the Comité de Protection des Personnes Nord Ouest III (ID-RCB: 2020-A02785-34). After publication of the results, access to MR images will be possible for testing other CAD systems.

Trial registration number NCT04732156.

Strengths and limitations of this study

- Prospective, multicentre, multivendor study making results more generalisable.
- Design close to routine management of the patient, making results more applicable to real-life clinical practice.
- Constitution of a large cohort of patients with a 3-year follow-up that will be made available for testing (and comparing) other computer-aided diagnosis/detection (CAD) systems, after publication of the study results.
- Ancillary study assessing Prostate Health Index (PHI) to determine the best diagnostic pathway combining PHI and MRI results.
- This study is limited by the retrospective analysis of magnetic resonance images by the CAD system, whose results will not be used for targeted biopsy; this may underestimate the accuracy of the CAD system.

INTRODUCTION

Prostate multiparametric MRI (mpMRI) has shown excellent results in detecting and localising prostate cancers with an International Society of Urological Pathology (ISUP) grade of ≥2.[1–6] As a result, the European Association of Urology guidelines now recommend, in case of clinical suspicion of prostate cancer, to perform a prostate mpMRI prior to any biopsy.[7] The main strength of prostate mpMRI lies in its excellent sensitivity of 0.91 (95% CI 0.83 to 0.95) in a recent systematic review using template biopsy as reference standard.[5] However, mpMRI suffers from two main limitations. First, in the same systematic review, its pooled specificity was only 0.37 (95% CI 0.29 to 0.46). This may induce useless targeted biopsy in a substantial proportion of men. Second, its inter-reader reproducibility is moderate at best, even when the Prostate Imaging-Reporting and Data system (PI-RADS) is used for interpretation.[8] Thus, the excellent results reported in large trials performed at experienced high-volume centres may not be reproduced in less-experienced institutions.

In this context, the optimal diagnostic pathway for patients with suspected prostate cancer remains unclear.[9–11] A first option would be to perform prostate biopsy systematically, regardless of mpMRI findings. Patients with positive mpMRI would undergo combined systematic and targeted biopsy; those with negative mpMRI would undergo systematic biopsy. This approach maximises the detection of clinically significant prostate cancer (csPCa), especially in biopsy-naïve patients, but results in substantial overdetection (and potential overtreatment) of insignificant cancers and in performing useless biopsy procedures in a large proportion of men.[3–5] The opposite option would be to use mpMRI as a triage test for prostate biopsy: patients with positive mpMRI would undergo only targeted biopsy, while those with negative mpMRI would not be biopsied at all. This approach, however, is limited by mpMRI low specificity. In addition, because of mpMRI moderate inter-reader reproducibility, csPCa detection may be suboptimal without the 'safety net' of systematic biopsy, at least in less-experienced centres.[12]

Patient selection for biopsy may be improved by combining MRI findings with simple clinical data or with other biomarkers. Among available biomarkers, the Prostate Health Index (PHI) has shown promising results in safely avoiding mpMRI and/or prostate biopsy in patients with suspected prostate cancer, at a reasonable cost.[13 14] In addition, artificial intelligence may help standardising prostate mpMRI interpretation. Many groups have recently published good results in characterising focal lesions seen on mpMRI with computer-aided diagnosis/detection (CAD) systems using conventional machine learning approaches or deep-learning techniques.[15–25] These CAD systems can either help characterising lesions outlined by the radiologist (computer-aided diagnosis (CADx) systems) or provide parametric maps highlighting suspicious regions that may correspond to cancers or aggressive cancers (computer-aided detection (CADe) systems). Some CAD systems have even been shown to improve human reading both in experienced and less-experienced readers, but mostly in single-institution studies, which makes it hard to extrapolate the results to other centres or MRI machines.[26–28] Indeed, these approaches suffer from a lack of robustness across imaging protocols and magnetic resonance (MR) vendors.[29–32] Of the many published CAD systems aimed at characterising focal MR lesions, only a few have undergone validation on cohorts from a different centre and a different vendor, with mixed results.[28 33–35] Therefore, algorithms providing robust findings on multicentre multivendor cohorts are still lacking.

Our group is developing CADe systems aimed at detecting aggressive prostate cancer on MR images based on quantitative imaging and deep-learning techniques, under the RHU PERFUSE research programme funded by the French National Research Agency (ANR-17-RHUS-0006).[25 33] These systems are trained using a multivendor radiological–pathological correlation database of prostate mpMRI performed before prostatectomy. The purpose of the CHANGE study is to build a large prospective multicentre multivendor cohort of patients assessed by prostate mpMRI and subsequent systematic and targeted biopsy. This cohort will be used for the final external validation of the best CAD system developed in the RHU PERFUSE programme, by evaluating its non-inferiority as compared with the PI-RADS V.2.1 score in predicting the presence of ISUP grade of ≥2 prostate cancer at systematic and targeted biopsy. As an ancillary study, PHI will be measured in all patients to evaluate how this biomarker could be used to select patients who could safely avoid prostate mpMRI and/or biopsy.

METHODS AND ANALYSIS

Research hypotheses

The primary hypothesis of the CHANGE study is that the area under the receiver operating characteristic curve (AUC) of the tested CAD system for predicting the presence of ISUP grade of ≥2 cancer at targeted and systematic biopsy, at patient level, will not be significantly inferior to that of the PI-RADS V.2.1 score.

As a secondary hypothesis, we also hypothesised that combining PHI and mpMRI findings would improve the selection of patients referred to prostate biopsy.

Study design

This is a prospective multicentre non-inferiority trial. Participants will be recruited in outpatient clinics by local urologists among patients referred for clinical suspicion of prostate cancer. Included patients will undergo prostate mpMRI and combined targeted and systematic biopsy. A blood sample will be taken before prostate biopsy for PHI assessment. When available (ie, at the end of the RHU PERFUSE programme), the final version of the CAD will be used to retrospectively assess the risk that the prostate harbours ISUP grade ≥2 cancer. CAD and biopsy findings will be compared at patient (primary objective), lobe and lesion levels. In addition, included patients will be followed up for 3 years, and any prostate cancer diagnosed during the follow-up period will be noted.

Study setting and population

Seventeen French academic or private centres with expertise in prostate mpMRI and targeted biopsy were invited to participate in this study. Patients referred for suspicion of prostate cancer, aged between 18 and 80 years, with a prostate-specific antigen (PSA) level of ≤30 ng/mL, a clinical stage ≤T2 c and affiliated to the French Social Security will be eligible. Exclusion criteria include history of prostate cancer, history of prostate biopsy performed less than 12 months before inclusion, history of pelvic radiotherapy (regardless of its indication), history of androgen deprivation therapy, history of hip prosthesis, contraindication to MRI or prostate biopsy, participation to another research with an ongoing exclusion period and incomprehension of the French language. Patients under guardianship or curatorship will also be excluded. One of the local investigators will introduce the trial to eligible patients who will receive verbal and written information before signing the ethics committee-approved consent form. Patients will be informed that their participation in the study is voluntary, that refusal to participate will not influence their future management and that they can withdraw from the study at any moment, without justification. To avoid any selection bias, patients will be included before undergoing prostate mpMRI, and included patients will undergo prostate biopsy regardless of the mpMRI results.

Procedures

Prostate mpMRI will be performed in compliance with the PI-RADS V.2.1 guidelines (https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2-1.pdf?la=en) and will include at least axial T2-weighted imaging, axial diffusion-weighted imaging with a maximal b value of ≥1400 s/mm² and axial dynamic contrast-enhanced (DCE) imaging after intravenous injection of a bolus of gadolinium chelates (0.1 mmol/kg) with a temporal resolution of ≤15 s. MR examinations will be interpreted by a local senior radiologist using PI-RADS V.2.1 criteria.[36] Focal lesions with a PI-RADS V.2.1 score of ≥2 will be noted on a standardised prostate diagram. For each lesion, the radiologist will assess its size and location (peripheral zone, transition zone or central zone), T2, diffusion and DCE categories using PI-RADS V.2.1 criteria, the overall PI-RADS V.2.1 score and the likelihood of extracapsular extension (five-level Likert score). The radiologist will also outline each lesion on T2-weighted, diffusion-weighted and DCE images. For each pulse sequence, delineation will be performed only on the section level considered the most representative of the lesion. The prostate lobes will be assigned the PI-RADS V.2.1 score corresponding to the highest score of the lesions they contain. The patients will be assigned the highest PI-RADS V.2.1 score of the two lobes. MR images and lesion outlines will be anonymised and transferred to the coordinating centre (Hospices Civils de Lyon).

A blood sample will be taken from included patients at least 3 weeks after any digital rectal examination or prostate manipulation, and less than 3 months before prostate biopsy. Samples will be centrifuged at the local laboratory and the serum will be stored at −20°C within 1 hour. If this is not possible, samples will be kept at +4°C and centrifuged and stored at −20°C, but no longer than 3 hours after blood sampling, as recommended.[37 38] The delay between blood sampling and storage at −20°C will be noted for each patient. Then, samples will be sent at −20°C to the coordinating centre, where they will be processed for PHI assessment. PHI will be calculated from the serum concentrations of total PSA, free prostate-specific antigen (fPSA) and [−2]proPSA using the following formula: $PHI = \frac{[-2]\text{proPSAx}\sqrt{PSA}}{\text{fPSA}}$. PHI results will not be available to local investigators at the time of biopsy, to avoid bias. At the end of the study, the remaining blood samples will be destroyed. No biological collection is planned.

Prostate biopsy will be performed by a senior radiologist or a senior urologist under transrectal ultrasound guidance, no longer than 3 months after prostate mpMRI and blood sampling for PHI determination. All lesions with a PI-RADS V.2.1 score of ≥3 will be targeted at biopsy. Targeted biopsy will be obtained according to the centre's routine technique, using cognitive guidance, software-assisted registration or direct targeting under high-frequency ultrasound guidance. The guidance technique for each patient will be documented. At least three biopsy cores will be taken from each targeted lesion to ensure proper sampling.[39 40] In addition, 12 systematic biopsies will be taken; however, for patient comfort, the biopsy operator will be free not to obtain systematic biopsy from prostate areas already sampled by targeted biopsy. Patients without any lesions with a PI-RADS V.2.1 score of ≥3 will undergo 12-core systematic biopsy. The total number of systematic and targeted cores will be noted for each patient. Prostate biopsy cores will be analysed by a local senior pathologist on a core-by-core basis. For each core, the presence of cancer and the core length will be noted. In addition, the ISUP grade group and the length of cancer invasion will be noted for each core containing cancer.

The evaluated CAD system will be the final CAD system developed under the RHU PERFUSE research programme. Its output will be, for each slice level, a parametric map providing a probability score that each pixel corresponds to ISUP grade ≥2 cancer. Parametric maps will be analysed at the end of the programme, and therefore, their results will not be known at the time of biopsy. The analysis of the CAD parametric maps will be performed by two radiologists from the coordinating centre, working in consensus, and who will be blinded to the biopsy and follow-up results. First, they will copy onto the CAD parametric maps the lesions' outlines drawn by the local radiologist on MR images. The mean CAD score of the pixels located within each lesion outline will correspond to the lesion's CAD score, for per-lesion analysis. Then, the two radiologists will define the CAD score of each lobe. It will correspond to the highest score of any lesion of ≥6 mm located in the lobe, whether it was seen by the local radiologist or not.[36]For per-patient analysis (primary analysis), the CAD score will be the highest score of both lobes.

Included patients will be followed up at least 3 years by local investigators. The date and type of treatment will be recorded for all patients treated by active therapy for prostate cancer (prostatectomy, radiotherapy, brachytherapy, high-intensity focused ultrasound, hormone therapy, etc) after the study biopsy. For patients with negative biopsy findings and for those managed by active surveillance, the date and results of any additional histological examination of prostate tissue (after additional prostate biopsy or transurethral prostate resection) will be recorded. Follow-up data will be collected from medical records or after a telephone interview with the patients.

Standard of reference

The results of the combined targeted and systematic biopsy performed within 3 months of the prostate mpMRI will be considered the histological standard of reference for per-patient and per-lobe analyses. For per-lesion analysis, only the results of targeted biopsy will be taken into consideration. csPCa will be defined as ISUP grade ≥2 cancer throughout the analysis.

Primary and secondary objectives

The primary objective will be the assessment of the non-inferiority of the AUC of the CAD score as compared with that of the PI-RADS V.2.1 score for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level.

Secondary objectives include (1) the comparison of the sensitivity and specificity of the CAD and PI-RADS V.2.1 scores for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at lesion, lobe and patient levels; (2) the comparison of the AUC, sensitivity and specificity of the CAD and PI-RADS V.2.1 scores for predicting the diagnosis of csPCa within the 3 years of follow-up, at patient level; (3) the assessment of the influence of the biopsy setting (biopsy naïve vs history of prior negative biopsy), magnetic field strength (1.5 T vs 3 T), experience (years) of the radiologist in assessing the PI-RADS V.2.1 score, guidance method (cognitive vs software-assisted registration) for targeted biopsy and prostate volume (in millilitre) on the AUC of the CAD and PI-RADS V.2.1 scores for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level; (4) the comparison of the AUC of PHI, the CAD score and the PI-RADS V.2.1 score for predicting the presence of csPCa at subsequent targeted and systematic biopsy, at patient level; and (5) the estimation of the number of avoided mpMRI and prostate biopsies and of the number of missed csPCa in various diagnostic pathways combining the use of PHI and mpMRI as triage tests (figure 1).

Data collection and assessment points

Patient recruitment will start in the first trimester of 2021 and is expected to last for 24 months. Table 1 summarises enrolment and intervention time points.

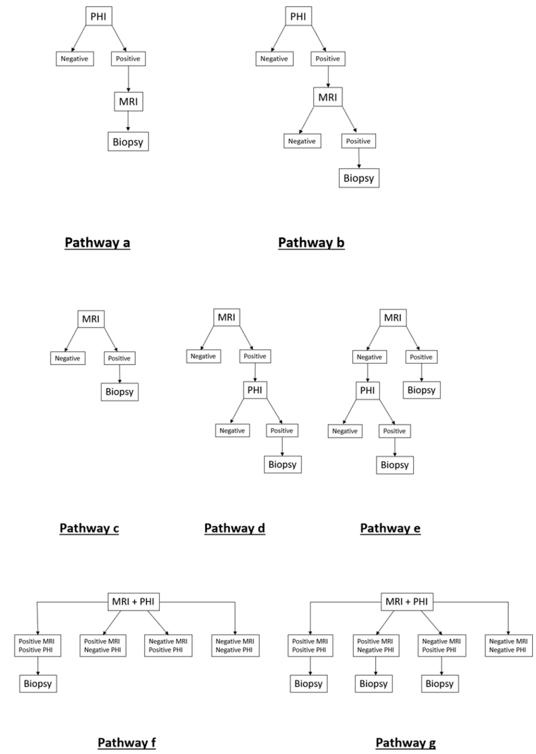

Figure 1 Possible diagnostic pathways using PHI, prostate MRI or the combination of both as triage tests. PHI, Prostate Health Index.

Data management, access and sharing

Only the data necessary to complete the protocol and the scientific publication will be collected, using an electronic case report form (eCRF). The eCRF will be developed by a data manager at the Hospices Civils de Lyon using the Ennov Clinical V.7.5.720 software that is compliant with the US Food and Drug Administration (FDA) guidelines on clinical trial management (Guidance for Computerised Systems Used in Clinical Trial—FDA-2004-D-0039) and on electronic signature (FDA 21CRF part 11). The dataset will be computerised in a coded way, in accordance with the Law for Data Protection and Freedom of Information. The study patients will be identified by a unique inclusion number and by the first initials of their surname and given name. The patient identification log will be kept in the investigator file. Data will be entered, as soon as they are collected, by the authorised persons using their own login names according to the Law for Data Protection and Freedom of Information. The investigator is responsible for the accuracy, quality and pertinence of all the data entered. As a result, each eCRF page will be electronically dated and signed by the investigator. On receipt of the data, the coordinating centre will check the eCRF and query all missing, implausible and inconsistent data.

This study falls within the framework of the 'Reference Methodology' (MR-001) under the provisions of Article 54, Paragraph 5, of modified French Law 78–17 from 6 January 1978, related to Information Technology, Files and Liberties. This alteration has been approved by the

Table 1 Time points of enrolment and interventions

	Enrolment (month 0)	Visit 1 (month 0)	Visit 2 (months 0–3)	Visit 3/end of study (month 36±2)
Informed consent and enrolment	X			
Assessment of patient history, clinical stage and PSA level	X			
Blood test (PHI)		X		
Multiparametric MRI		X		
Targeted biopsy based on human reading of magnetic resonance images (PI-RADS V.2.1)			X	
Systematic biopsy			X	
Assessment of adverse events		X	X	X
Assessment of 3-year follow-up				X

PHI, Prostate Health Index; PI-RADS V.2.1, Prostate Imaging-Reporting and Data System version V.2.1; PSA, prostate-specific antigen.

decision made on 5 January 2006 and modified on 21 July 2016. The Hospices Civils de Lyon, sponsor of the study, has signed a commitment of compliance to this Reference Methodology.

A trial steering committee presided by the study coordinator and composed of the scientists, biologists, methodologists, biostatisticians and coordinators involved in defining the study design and protocol will oversee the final version of the protocol, the conduct of the trial and the redaction of the publication. It will also validate and justify any change in the study protocol or statistical analysis plan.

Sample size

The calculation of the sample size was performed according to the method described by Zhou *et al*.[41] The AUC of the PI-RADS V.2.1 score at patient level is expected to be 0.85.[42] Under the hypothesis of equality of the AUC of the CAD and PI-RADS V.2.1 scores, for a non-inferiority margin of −5%, a bilateral alpha risk of 5% (one-sided significance level of 2.5%), an expected prevalence of csPCa of 30%,[3–5] and a correlation of 0.3 between the CAD and PI-RADS V.2.1 scores in patients with csPCa and in those without csPCa, the inclusion of 385 patients will allow assessment of the non-inferiority of the CAD score with a statistical power of 80%. To account for 10% of excluded patients, the trial will include 420 patients.

Statistical analysis

Analysis will be performed by a professional statistician from the Department of Biostatistics of the Hospices Civils de Lyon. A statistical analysis plan will be written before the database lock. It will consider any unexpected event or change in protocol with impact on data analysis. Any change in the statistical analysis plan occurring after the database lock will be documented and justified.

Data will be analysed according to the intention-to-treat principle (ie, all patients who underwent both mpMRI and prostate biopsy will be included). In case of major protocol deviations, an additional per-protocol analysis will be performed after exclusion of the patients with major deviations. The list of major deviations will be established after review of the data and specified in the statistical analysis plan.

For the primary objective, the AUC of the CAD and PI-RADS V.2.1 scores will be estimated at patient level using the binormal method, along with their 95% CIs. The difference between the AUC of the CAD and PI-RADS V.2.1 scores will be estimated with its 95% CI. Non-inferiority will be established if the lower limit of the 95% CI of the AUC difference is superior to −5%.

For secondary objectives, the specificity and sensitivity of the PI-RADS V.2.1 score at patient, lobe and lesion levels will be estimated using a positivity threshold of ≥3. The CAD scores will be estimated using the threshold yielding a sensitivity of 90% in the training database. The Wilson method will be used to calculate the 95% CIs for sensitivities and specificities. Sensitivities and specificities of the CAD and PI-RADS V.2.1 scores will be compared using the McNemar test. Positive and negative likelihood ratios and their 95% CIs will also be estimated for both tests. The effect of biopsy setting, magnetic field strength, reader's experience, guidance method for targeted biopsy and prostate volume on the AUC of the final CAD and the PI-RADS V.2.1 scores will be quantified by modelling the receiver operating characteristic curve using a probit regression model.[43]

The AUC of PHI will be estimated and compared with the AUC of the CAD score and the PI-RADS V.2.1 score, respectively, using the binormal method. The following PHI positivity cut-offs will be used to assess different diagnostic pathways (figure 1): 25 when PHI is used as an upfront diagnostic test (pathways a and b) or in combination with MRI (pathways f and g), and 50 when PHI is used in as a second-line test after mpMRI (pathways c–e). The different diagnostic pathways will be applied to the studied population to predict the number of avoided mpMRI, avoided biopsies and missed csPCa. These numbers will be given with a predicted interval, taking into account the uncertainty on the estimate of the diagnostic performance of the tests.

Patient and public involvement

Patients and the public were not involved in the design of this study.

DISCUSSION

The CHANGE study is aimed at constituting a prospective multicentre multivendor cohort of patients with suspected prostate cancer who underwent prostate mpMRI and subsequent targeted and systematic biopsy. This cohort will be used for external validation of the final CAD system developed under the RHU PERFUSE research programme. For this study, we made four main methodological choices.

First, we chose not to include patients with scheduled prostatectomy, although this would have allowed comparison of CAD findings to a solid histological ground truth. Indeed, patients treated by prostatectomy constitute a biased population with a 100% prevalence of prostate cancer. Instead, we chose to study the real target population of any CAD aimed at diagnosing csPCa on MR images: patients with clinical suspicion of prostate cancer referred for prostate biopsy. We did not include patients under active surveillance. Thus, our results may not be applicable to this population.

Second, we decided to use the results of targeted and systematic biopsy as standard of reference, although it may miss some csPCa. Using a more sensitive biopsy technique such as transperineal template saturation biopsy would have improved the detection of csPCa. However, template saturation biopsy is not obtained routinely in France. In addition, the clinical significance of cancers with an ISUP grade of ≥2 detected by such sensitive an approach remains debated. Therefore, we chose to use as standard of reference the biopsy technique that is recommended for prostate cancer diagnosis in daily routine.[7]

Third, patient recruitment will start before the CAD is finalised, and thus, the CAD will not be used to trigger targeted biopsy. This results from a pragmatic choice. Setting a prospective study in which the CAD is used to trigger targeted biopsy would need a CAD system that has good and stable results on its training databases, is embedded in an easy-to-instal, user-friendly interface, and has gone through all legal and regulatory requirements for clinical use. It was unrealistic to develop such a CAD system and then to perform a multicentre validation study within the duration of the RHU PERFUSE programme. Instead, we preferred recruiting a multicentre prospective cohort while the CAD was being developed. We acknowledge that comparing the accuracy of the CAD and the PI-RADS V.2.1 scores in this cohort will be to the disadvantage of the CAD score. Indeed, the CAD system may show some cancer foci missed by human reading and subsequent biopsy and that will be erroneously considered as CAD false positive findings at per-lobe and per-patient analyses. To mitigate this, we included a 3-year follow-up for patients with negative biopsy. Nonetheless, such a design also has advantages. Because no particular CAD system will be used to trigger targeted biopsy, our cohort may be used as a reference cohort for evaluating other CAD systems. Therefore, our data sharing policy stipulates that the cohort will be made accessible to other research groups, as a test cohort, once our own CAD system has been evaluated. We hope that this will allow rapid comparisons between artificial intelligence solutions in a challenging multicentre multivendor setting. Furthermore, although the CHANGE cohort is primarily designed for testing algorithms developed on mpMRI datasets, it is also suitable for testing CAD systems aimed at assessing biparametric MRIs. In such case, the DCE datasets will be removed from the cohort and the lesions' PI-RADS scores will be calculated without considering the DCE category, as detailed in the PI-RADS V.2.1 guidelines. Finally, the definition of csPCa is currently highly controversial.[44] Our primary objective will be assessed using the definition currently used in most studies (ISUP grade group ≥2). Nonetheless, because we collected the ISUP grade group and the length of cancer invasion on a core-by-core basis, alternate definitions for csPCa could be easily used.

Our fourth methodological choice was to measure PHI in all patients. This ancillary study is independent of the evaluation of the CAD system. However, we took advantage of constituting a prospective multicentre cohort to also assess whether PHI could be used, as a stand alone or in combination with mpMRI, to select patients who could safely avoid mpMRI and/or prostate biopsy, thereby reducing both patient discomfort and the cost of prostate cancer diagnostic pathway. Other simple biomarkers such as PSA density or PHI density can also be easily calculated from the database. Including them in combination with PHI and MRI would have resulted in too many possible diagnostic pathways. A large body of literature is available on PSA density, although the way it should be combined with MRI and the optimal diagnostic threshold remain unclear.[45,46] Nonetheless, there may be guidelines for the use of PSA density when the inclusions are completed. Similarly, whether PHI density is useful is currently unclear,[14] but this may be clarified by the end of the inclusions. If this is the case, the statistical analysis plan, written at the end of the inclusions but before the database is accessed, may include PSA density and/or PHI density in the tested diagnostic pathways.

ETHICS AND DISSEMINATION

Ethical approval was obtained from the Comité de Protection des Personnes Nord Ouest III (ID-RCB: 2020-A02785-34) on 22 January 2021. The study was registered with ClinicalTrials.gov. The Hospices Civils de Lyon is the responsible institution for this trial. The study coordinator will coordinate dissemination of the trial data through scientific conferences and publications in peer-reviewed international journals. Data reporting will follow the Standards for the Reporting of Diagnostic Accuracy Studies guideline.[47]

As specified in the informed consent form signed by the patients, the CHANGE cohort will be made partially accessible to other investigators wishing to test a CAD system aimed at detecting/localising prostate cancer on MR images, once the results of the trial have been published. Request for access to pseudonymised data will be reviewed by the trial steering committee that will grant access or not. To gain access, requestors will need to sign a data access agreement. Of note, investigators will have access only to the MR images and not to the histological findings. After analysis of the CHANGE MR images by their CAD system, investigators will be requested to send the results to the Hospices Civils de Lyon. The comparison between the CAD findings and the targeted and systematic biopsy findings will be made by the Hospices Civils de Lyon that will then inform the investigator of the CAD diagnostic performance.

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Contributors All authors contributed to the design of the study and to the formulation of the protocol. OR is the principal investigator for this trial and has initiated and planned this trial project with SC. SC is the medical coordinator of the RHU PERFUSE Research programme and CM is the scientific project manager coordinating the different work packages of the programme. RS, CL, TJ and AD are developing and testing different approaches for the CAD systems as senior scientists (RS and CL) or PhD students (TJ and AD). RS is also responsible for the quality control of the magnetic resonance (MR) examinations performed in the participating centres. JH oversaw the study design. MR and BR are biostatisticians. MR played a central role in the sample size calculation and will write the statistical analysis plan. AM, LM, MC, MD-C and SD drafted the protocol and will play a central role in study coordination, data management and in providing support to the participating centres. PR designed the electronic case report form. VV-G participated in the design of the ancillary study and is responsible for supervising the management of blood samples and the dosage of PHI.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

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